Original Research

# Applicability of the ROX index in decision-making for hospitalization in COVID-19 patients

ROX index in the outpatient COVID-19 cases

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## Abstract

Aim: Data on the outpatient follow-up of COVID-19 cases is still scarce. Also, the significance of the ROX index in decision-making for hospitalization in the ambulatory COVID-19 cases remains unknown. The aim of this study is to determine the general characteristics of COVID-19 patients treated as outpatients and to investigate whether the ROX index is applicable in hospitalization decisions.

Material and Methods: This retrospective cohort study was conducted in confirmed adult COVID-19 cases between 15 October 2020 and 01 March 2021. A total of 5240 confirmed COVID-19 patients were included in the present study. Factors affecting hospitalization were investigated.

Results: The study population was divided into two groups as those who require hospitalization (n=672) and those who did not (n=4568). The number of male patients and the mean age of the patients were significantly higher in hospitalized patients group (p=0.046, p<0.001). ROX index that was calculated at the home visit on the third day of disease was found significantly lower in the group of hospitalized patients (p<0.001). There was a significant correlation between ROX index and inflammatory biomarkers in the present study (p<0.001). The ROX index was found the most accurate parameter for decision-making for hospitalization in ambulatory COVID-19 patients (AUC=0.794 CI=0.773-0.814, p<0.001).

Discussion: The ROX index can be a useful and objective clinical tool for decision making for hospitalization in the ambulatory COVID-19 cases.

## Keyword:

COVID-19, Ambulatory, Hospitalization, Predictors, ROX Index

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## Introduction

In the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), approximately 80% of the cases have mild disease that do not require hospitalization, and these cases can be followed up in ambulatory settings [1, 2]. However, data on the outpatient follow-up of COVID-19 cases is still scarce, and clinical experience from the onset of the pandemic to the present forms the bulk of current strategies. Patient management in COVID-19 outpatients includes early initiation of antiviral treatment, supportive care, measures to reduce the risk of SARS-CoV-2 transmission, and recommendations on when patients should present to the hospital [3].

Although the risk of hospitalization and mortality is higher in the elderly and comorbid COVID-19 cases, COVID-19 severe illness and death can occur in any age group. As a result, early diagnosis of potentially sudden clinical deterioration in outpatients is a critical step in patient management. To this end, clinicians need quick and easy diagnostic tools to support their clinical decisions [1, 4].

The ROX Index (Respiratory rate-OXygenation) was developed by Roca et al. in 2016 to evaluate the success of high flow nasal cannula (HFNC) oxygen therapy. The ROX index is calculated by dividing the peripheral oxygen saturation (SpO2) by the fraction of inspired oxygen (FiO2) and the respiratory rate (RR). It has been shown that a ROX index of <4.88, calculated 12 hours after initiation of HFNC therapy, is associated with a high risk of intubation [5, 6].

The significance of the ROX index in decision-making for hospitalization in the ambulatory COVID-19 cases remains unknown. This study aimed to determine the general characteristics of COVID-19 patients treated as outpatients and to investigate whether the ROX index is applicable in hospitalization decisions.

# Material and Methods

Study design

This study protocol was approved by the Turkish Ministry of Health and Clinical Ethics Committee of Inonu University (protocol code:2021/2142). The retrospective cohort study comprised patients over 18 years of age who were diagnosed with COVID-19 between 15 October 2020 and 01 March 2021 in Malatya followed up and treated at home.

Exclusion and inclusion criteria

Inclusion criteria for the study included confirmed COVID-19 cases, cases aged 18 years and older. Exclusion criteria for the study included suspected COVID-19 cases, non-COVID-19 patients, patients with missing data, and patients aged <18 years.

Data collection and definitions

A confirmed case of SARS-CoV-2 infection was defined as follows: a symptomatic case with positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) from the nasopharyngeal and/or oropharyngeal swab, and/or an asymptomatic person with a positive SARS-CoV-2 RT-PCR who is a contact of a probable or confirmed case.

COVID-19 cases treated at home were examined on the 3rd day after a positive PCR test result for COVID -19 by a team

consisting of a doctor and a nurse from the Malatya Provincial Health Directorate. Vital signs of COVID-19 cases on the day of their home assessment include diastolic blood pressure (mmHg), systolic blood pressure (mmHg), respiratory rate (breaths per minute), oxygen saturation in the room air (%), heart rate (beats per minute), body temperature (C), and Glasgow Coma Scale), initial symptoms, demographics, comorbidities, laboratory data (including complete blood count, glucose, urea, creatinine, albumin, aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin, sodium (Na), chloride (Cl), potassium (K), C-reactive protein (CRP), D-Dimer, cardiac troponin I (cTnI), ferritin ), ROX indices, and hospitalizations were recorded. Patients' oxygen saturation in the room air and heart rate were measured for 1 minute with the same pulse oximetry device (Covidien Nellcor™ Bedside SpO<sub>2</sub> Patient Monitoring System), while the patient resting in a sitting position for 15 minutes. Statistical analysis

We used the SPSS (Statistical Package for Social Sciences) program for macOS 25.0 for the statistical analysis. Normally and homogeneously distributed variables are reported as mean± and standard deviation, data that do not have a normal and homogeneous distribution are reported as median (min-max), categorical variables are reported as numbers and percentages. When comparing two independent groups, the independent variable t-test was used when analyzing parametric data. The Mann-Whitney U test was used when analyzing nonparametric data. The Chi-Squared test was used when analyzing categorical data. The prediction performance of the parameters for the hospitalization was evaluated by calculating the area under the curve (AUC), the receiver operating characteristic (ROC) curve. The study used the ROC curve to determine the appropriate cutoff value of the parameters. Independent variables associated with hospitalization in the univariate analysis were evaluated with multivariate logistic regression models. Odd ratio and 95% confidence interval (CI) were calculated with the "Enter" method. Pearson's correlation analysis was used for the examination of the correlation between the ROX index and inflammatory parameters. The results were analyzed with a 95% confidence interval and a significance level of p<0.05

## Results

Baseline general characteristics of the study population

A total of 5240 confirmed COVID-19 patients were included in the present study. The study population was divided into two groups as those who require hospitalization (n=672) and those who did not (n=4568). In the group of hospitalized patients, the number of male patients and the mean age of the patients were significantly higher (p=0.046, p<0.001). Coronary artery disease (CAD) (5.8% vs 3.1%) and chronic obstructive pulmonary disease (COPD) (11.3% vs 5.8%) were found significantly higher in the group of hospitalized patients respectively (p<0.001, p<0.001) (Table 1).

The proportions of the patients with dyspnea, fatigue, cough and fever were significantly higher in the group of hospitalized patients compared with the non-hospitalized patients (p=0.001, p=0.022, p<0.001, p=0.005). At the home visit on the third day of the course of the disease, the respiratory rate and heart rate

were significantly higher in the group of hospitalized patients (p<0.001, p<0.001). Also, oxygen saturation measured in room air was significantly lower in the group of hospitalized patients compared with the non-hospitalized patients (p<0.001). Moreover, the ROX index calculated at the home visit on the third day of disease was found to be significantly lower in the group of hospitalized patients compared with non-hospitalized patients (p<0.001) (Table 1).

Lymphocytes and platelets level were significantly lower in the group of hospitalized patients (p<0.001, p<0.001). Also, the level of serum albumin was significantly lower in the group of hospitalized patients compared with non-hospitalized patients (p<0.001). Moreover, level of inflammatory markers including serum CRP and ferritin were found significantly higher in the group of hospitalized patients compared with non-hospitalized patients (p<0.001, p<0.001) (Table 2). Also, there was significantly negative correlation between ROX index and inflammatory biomarkers including serum CRP, LDH and ferritin level in the present study (p<0.001).

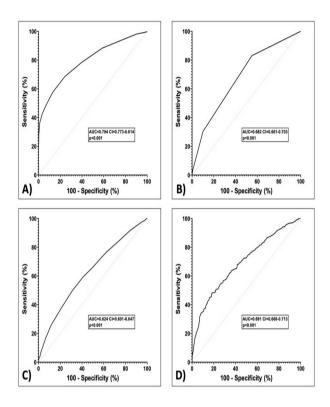
Table 1. Baseline characteristics of the patients

		Hospitalization		
		No (n=4568)	Yes (n=672)	P value
Age, years		61.62±11.53	69.65±10.86	<0.001
Gender	Male, n (%)	2458 (53.80%)	334 (49.70%)	0.055
	Female, n (%)	2110 (46.20%)	338 (50.30%)	
At least one comorbidity	Yes, n (%)	2621 (57.4%)	471 (70.10%)	<0.001
	No, n (%)	1947 (42.6%)	201 (29.90%)	
	HT, n (%)	1734 (84.25%)	324 (15.75%)	<0.001
Comorbidities	DM, n (%)	1028 (82.17%)	223 (17.83%)	<0.001
	Malignancy, n (%)	62 (80.51%)	15 (19.49%)	0.078
	COPD, n (%)	266 (77.77%)	76 (22.23%)	<0.001
	CAD, n (%)	143 (78.57%)	39 (21.43%)	<0.001
	Hypothyrodism, n (%)	103 (91.96%)	9 (8.04%)	0.125
Smoking status	Ex-smoking, n (%)	353 (7.74%)	67 (9.97%)	
	Currently smoking, n (%)	470 (10.28%)	28 (4.16%)	<0.001
	Never smoked, n (%)	3745 (81.98%)	577 (85.87%)	
Symptoms	Myalgia, n (%)	2148 (47.00%)	309 (46.00%)	0.614
	Fatigue, n (%)	1941 (42.50%)	317 (47.20%)	0.022
	Cough, n (%)	1465 (31.10%)	280 (41.70%)	<0.001
	Fever, n (%)	1159 (25.40%)	205 (30.50%)	0.005
	Headache, n (%)	761 (16.79%)	94 (14.00%)	0.080
	Dsypnea, n (%)	395 (8.60%)	105 (15.60%)	<0.001
Vital signs	Body temperature, oC	36.27±0.24	36.34±0.28	0.005
	SBP, mmHg	118.78±17.52	119.12±17.34	0.681
	DBP, mmHg	73.26±10.04	71.96±9.95	0.507
	MAP, mmHg	88.43±13.99	88.25±11.62	0.778
	RR, breaths/min	21.75±3.26	23.32±3.66	<0.001
	HR, beats/min	86.39±13.06	92.71±14.71	<0.001
	SpO2, percentage	96.63±1.82	92.54±4.88	<0.001
CURB-65, (Mean±SD)		0.66±0.67	1.17±0.75	<0.001
ROX index, (Mean±SD)		21.65±3.40	19.37±3.33	<0.001

DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, CHF: Chronic Heart Failure, CAD: Coronary Artery Disease, CVD: cerebrovascular disease, Cl: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, SpO2: Oxygen saturation, RR: Respiratory rate, HR: Heart rate, CURB-65: Confusion, uremia, respiratory rate, blood pressure, age ≥ 65 years, ROX: Respiratory rate—OXygenation

Predictors of hospitalization

We performed ROC analysis to predict hospitalization n performance of the parameters including respiratory rate, ROX index, CURB-65 score, and the oxygen saturation measured in



**Figure 1.** Receiver operator characteristics curve analysis of (A) ROX index (B) CURB-65 score (C) respiratory rate (D) oxygen saturation measured in the room air for decision making for hospitalization in the ambulatory COVID-19 cases

Table 2. Laboratory findings of the patients

		Hospita	P value	
		No (n=4568)	Yes (n=672)	
Complete blood count	Wbc, 103/µL (Min-max)	5.33 (1.66-21.46)	5.86 (2.22-18.39)	<0.001
	Lymph, 103/μL (Mean±SD)	1.78±0.66	1.48±0.59	<0.001
	Platelets, 103/μL (Mean±SD)	209.25±63.31	198.96±68.36	<0.001
	Hgb, g/dL (Mean±SD)	14.11±1.57	13.89±1.66	0.003
Biochemical parameters	Urea, mg/dL (Min-max)	27 (3-111)	32 (9-142)	<0.001
	Creatinin, mg/dL (Min-max)	0.83 (0.02-6.92)	0.89 (0.57-4.07)	<0.001
	AST, U/L (Min-max)	27 (1-333)	31 (11-324)	<0.001
	ALT, U/L (Min-max)	23 (6-422)	26 (6-381)	0.001
	LDH, IU/L (Mean±SD)	271.58±109.26	329.02±128.53	<0.001
	Albumin, g/dL (Min-max)	3.80 (1.90-4.80)	3.60 (1.60-4.70)	<0.001
CRP, mg/dL (Min-max)		0.70 (0.02-24.80)	3.20 (0.10-28.20)	<0.001
Ferritin, ng/dL (Min-max)		127.80 (3-2000)	204.30 (5-2000)	<0.001
Trop-I, ng/mL (Min-max)		0.10 (0.01-1.20)	0.15 (0.10-4.89)	<0.001
D-Dimer, μg/mL (Min-max)		0.29 (0.01-18.20)	0.42 (0.01-17.30)	<0.001

Wbc: White blood cells, Lymph: Lymphocytes, Hgb: Hemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C reactive protein, Trop-I: Troponin-I

the room air. Analysis of the ROC showed that the ROX index (AUC=0.794, p<0.001) was superior to the CURB-65 (AUC=0.682, p<0.001), respiratory rate (AUC=0.624, p<0.001), and oxygen saturation measured in the room air (AUC=0.691, p<0.001) for the prediction of hospitalization. Also, the cut-off value of ROX index was found 20.00 for the prediction of the hospitalization. For the prediction of hospitalization, among the compared parameters, the ROX index was found to be the most accurate parameter for decision-making regarding hospitalization in the ambulatory COVID-19 patients (Figure 1). Multivariate logistic regression analysis was performed for the prediction of the hospitalization. ROX index and age were independent predictors in decision making for hospitalization, respectively (OR=1.412 95% CI=1.239-1.978 p<0.001, OR=1.108 95% CI=0.988 -1.086, p<0.001).

# Discussion

The current study revealed that the ROX index was the most accurate parameter for the prediction of hospitalization. We believe that patients with a lower ROX index (<20.0) should be followed carefully and closely in the outpatient settings.

In clinical studies examining risk factors for hospitalization and mortality in COVID-19 cases, it was found that the rate of hospitalization due to COVID-19 was higher in men than in women, and correspondingly, the mortality rate was higher in men. However, other studies have found that mortality rates do not differ by patient gender [7-9]. In clinical studies conducted since the onset of the pandemic, age and comorbidity have been shown to be essential determinants of hospitalization, illness severity, and mortality in COVID-19 cases. Hospitalized patients have been shown to be older than outpatients with COVID-19. In addition, the course of COVID-19 disease has been shown to be more severe in elderly patients, and the mortality rate is higher in elderly patients. In addition, the prevalence of comorbidities has been shown to be higher in hospitalized COVID-19 cases and, more importantly, the disease was more severe, and the mortality rate was higher in COVID-19 cases with comorbidities [2, 8-11]. No statistical difference in gender was identified in hospitalized COVID-19 cases in our study, in which mortality rates were not evaluated. However, in the present study, in accordance with the literature, hospitalized COVID-19 cases were older than those who were not hospitalized, and 70% of hospitalized cases had at least one comorbid condition. However, although patient age was a significant risk factor for hospitalization in our study, comorbidity was not an independent risk factor.

The rapid increase in the number of cases has led to a significant increase in demand for hospital beds and a shortage of medical equipment, resulting in the collapse or shortages of healthcare systems worldwide [13]. To reduce the burden on healthcare systems while providing the best possible care to patients, it is necessary to quickly and accurately identify low-risk patients who can be followed at home or high-risk patients who need to be hospitalized. Furthermore, early detection of possible disease progression and early salvage treatment initiation in outpatient COVID-19 cases are essential steps in treating patients [1, 4, 13, 14]. Many new risk assessment models for COVID-19 have been developed, or scoring systems

previously designed for sepsis or pneumonia have been used for this purpose. However, all these models carry a high risk of bias. Therefore, clinicians need objective, rapid, and simple risk assessment tools to support their clinical decisions [13-15].

The CURB-65 score, developed by Lim WS et al., is a scoring system designed to identify patients at high risk of mortality from community-acquired pneumonia [16]. Thanks to this scoring system, it is also easy to determine, which case requires inpatient treatment. While pneumonia cases with CURB-65 scores of 0 and 1 can be followed up on as outpatients. pneumonia cases with a CURB-65 score of ≥2 should be hospitalized and treated. In addition, studies have shown that mortality is higher in patients with the CURB-65 score ≥2 community-acquired pneumonia [15-17]. During the pandemic, most clinical studies examining the applicability of the CURB-65 score in COVID -19 cases were conducted in hospitalized COVID-19 cases. The success of CURB-65 in predicting hospital mortality and transfer to ICU has produced contradictory results [15, 18, 19]. In addition, the applicability of CURB-65 in deciding hospitalization in outpatient COVID-19 cases is not clearly known [17]. In our study evaluating the general characteristics of outpatient COVID-19 cases, the success of CURB-65 in predicting hospitalization lagged behind the ROX index, although hospitalized COVID-19 cases had a higher CURB-65 score.

The ROX index, developed by Roca et al. to assess the success of HFNC in critically ill patients is a simple and quick tool to calculate and reproduce [4, 5]. Low ROX index values (ROX index < 4.88), calculated particularly after initiation of HFNC therapy, have been shown to be associated with a high risk of intubation [5, 6]. It was found that the ROX index can be an applicable and useful predictor for intubation decisions and evaluation of HFNC success in clinical studies evaluating the applicability of the ROX index in cases of COVID-19 pneumonia treated with HFNC therapy during the pandemic [20].

Although the ROX index is a parameter that is easy to calculate and repeat in clinical practice and does not require laboratory results, there are few clinical studies examining its applicability in deciding hospitalization in COVID-19 cases. In the study by Gianstefani A et al., the ROX index was shown to have higher accuracy in estimating hospitalization than respiratory rate alone in COVID-19 cases presented to the emergency department. Furthermore, the study demonstrated that the ROX index (ROX index < 25.7) is an effective tool to distinguish patients who presented to the emergency department because of COVID-19 and require hospitalization from those who can be safely discharged. In addition, lower ROX index values have been shown to be associated with increased mortality in COVID-19 cases presented to the emergency department [4].

We found that the ROX index was statistically significantly lower in hospitalized patients than in outpatients. In addition, the ROX index was found to have a significant correlation with inflammatory parameters, which have been associated with disease severity and mortality in many previous clinical trials in COVID-19 cases, and to have higher accuracy in estimating hospitalization than respiratory rate and CURB-65 alone. More importantly, the risk of hospitalization increased 1.56-fold in patients with a lower ROX index (ROX index <20.0).

#### Conclusion

We found that the ROX index is the most accurate predictor of requirement for admission to the hospital rather than ambulatory care. Another identifiable risk factor for hospitalization includes the patient's age. The ROX index can be a useful and objective clinical tool for making hospitalization decision in the ambulatory COVID-19 cases, regardless of the radiological and laboratory findings. In addition, the ROX index may be a parameter that can be readily used in triage practice and patient management of COVID-19 cases presented to the emergency department and outpatient clinic. However, further clinical studies are required to confirm these findings.

## Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

## Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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## Conflict of interest

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